



Worsening of obstructive sleep apnoeas in a patient with rheumatoid arthritis treated with anti-tumor necrosis factor

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KEYWORDS

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Summary We report on a case of an adult patient treated for rheumatoid arthritis with infliximab, a chimerical monoclonal antibody to TNF α . Apart from this, the patient also showed clinical signs of obstructive sleep apnea syndrome that was confirmed by polysomnographic study. After infliximab treatment, additional sleep studies revealed an increase in the number of apneic events and SaO₂ dips suggesting that TNF α plays an important role in the pathophysiology of sleep apnea. Thus, clinical recognition of sleep disordered breathing should be taken into account when rheumatoid arthritis patients are to be treated with infliximab.

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Introduction

Tumour necrosis factor- α (TNF α) is a cytokine that plays an important role in the pathogenesis of rheumatoid arthritis (RA), and blocking strategies.¹ In patients with long standing RA and high disease activity despite conventional treatment, infliximab, a chimerical monoclonal antibody to TNF α , has been shown to be clinically effective.²

TNF α is also involved in sleep regulation³ as well as in the pathogenesis of obstructive sleep apnea (OSA).^{4–6} Therefore, the use of TNF α antibodies may help define the role of cytokines in OSA.

We report on a case of an adult patient with RA and who was treated with infliximab. The patient also had a condition of OSA and the result of the infliximab treatment was an increased number of apneic events and SaO₂ dips.

Case report

A 62-year-old woman was referred to the Rheumatology Division for treatment with infliximab. She had a 19-year-history of RA, according to the standard criteria.⁷ Cervical spine radiographs showed no evidence of significant atlantoaxial subluxation. The patient reported frequent nocturnal awakenings with a sensation of choking, snoring, unrefreshing sleep, daytime sleepiness and fatigue for 2 years. Her Epworth sleepiness

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Table 1 Sleep parameters before (Days 1 and 2) and during treatment with infliximab (Day 3).

	Before treatment		After treatment
	Day 1	Day 2	Day 3
Total sleep time (min)	396	419	346
Sleep efficiency (%)	67	84	80
Sleep latency (min)	24	30	27
Stages I + II (%)	80	78	88
Stages III + IV (%)	16	11	6
Stage REM (%)	4	11	6
Arousals/h	14	17	4
Mean SaO ₂ (%)	88	91	86
Minimum SaO ₂ (%)	70	81	52
ODI4	59	46	198
Mean heart rate (bpm)	72	69	64
Obstructive apnea count	54	137	212
Hypopnea count	226	196	175
AHI	47	49	74

ODI4: (oxygen desaturation index, indicates events with falls of SaO₂ ≥ 4% per night); Mean SaO₂ (%): Mean SaO₂ during desaturation during the recording; Minimum SaO₂ (%): Minimum SaO₂ during the recording; AHI: Apnea hipopnea index.

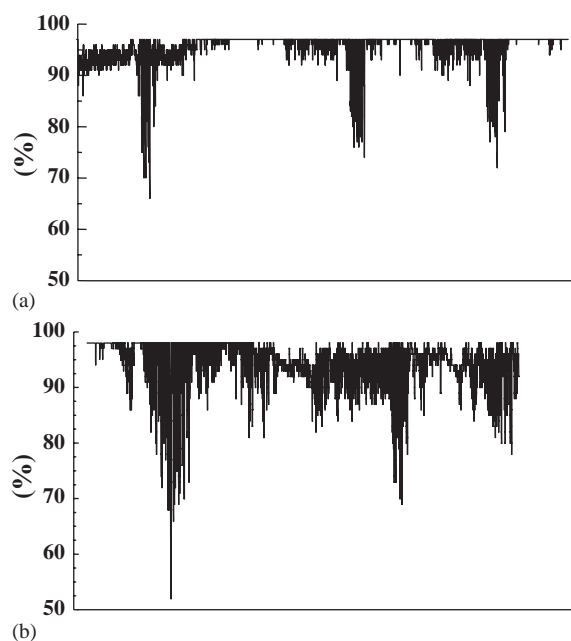


Figure 1 Two trends of SaO₂ before (a) and after infliximab treatment (b). After infliximab treatment the oximetric pattern shows greater desaturations.

score was abnormal. Physical examination showed obesity (BMI = 31 kg/m²), severe deforming arthritis of multiple joints with no active synovitis, and absence of dental malocclusion.

Two polysomnographic studies were carried out and the diagnosis of OSA was confirmed (Table 1). Afterwards, infliximab (3 mg/kg of body weight) was applied normally as a treatment for the RA. Additional sleep studies were performed revealing

a clear worsening of the condition after the application of infliximab. There was an increase in obstructive apneas and hypopneas, as well as oxygen desaturation index (SaO₂ dips), and a worsening of the sleep oxymetric pattern; on the other hand, the number arousal decreased (Fig. 1, Table 1). In response to this, overnight continuous positive airway pressure (CPAP) was started and infliximab treatment was maintained which resulted in the elimination of the respiratory events.

Discussion

In RA patients, sleep apnea can be caused by narrowing of upper airway, either by changes in the temporomandibular joints and the position of cervical vertebrae.⁸ In our case, however, clinical and radiological examination did not show these disturbances. Therefore, it is our opinion that this patient presented both RA and sleep apnea coincidentally, that is, the diseases were not associated. The infliximab treatment for RA may have worsened an already existing OSA, as evidenced by the increased number of apneic events and SaO₂ dips after infliximab treatment. Polysomnographic studies indicated no changes in body position or sleep stages before and after infliximab treatment.

The reasons why infliximab worsens the apneas and SaO₂ dips in our OSA patient while improving arousals remains obscure but a hypothesis which involves the role of TNF α to explain this seemingly contradictory finding can be advanced.

The worsening of OSA can be associated to the effect of $\text{TNF}\alpha$ on leptin. Finck et al.⁹ have shown that $\text{TNF}\alpha$ induces leptin production. Also, leptin circulating levels have been shown to be positively correlated with apnea–hypopnea index and $\text{TNF}\alpha$ ⁶ and leptin levels decrease after CPAP treatment.¹⁰ Therefore, it is possible that blocking $\text{TNF}\alpha$ with infliximab reduces leptin and that this leptin deficiency plays a role in the major desaturations experienced by OSA patients.^{11,12} On the other hand, in OSA patients some authors have shown that $\text{TNF}\alpha$ is positively correlated with the degree of hypoxia and the degree of nocturnal sleep disturbance and may mediate the daytime sleepiness associated with this disorder, independent of obesity.^{5,6} Moreover, in patients with RA and elevated circulating levels of $\text{TNF}\alpha$,¹³ sleep fragmentation and frequent arousals with marked disruption of sleep continuity can occur.¹⁴ Thus, $\text{TNF}\alpha$ seems to be involved in sleep fragmentation and arousability. It is known that $\text{TNF}\alpha$ may signal the central nervous system via vagal afferents¹⁵ and vagus nerve stimulation may influence respiration via central projections to the reticular formation of the medulla or medial pons.¹⁶ By interfering with this mechanism, the anti- $\text{TNF}\alpha$ treatment may decrease the arousal response to the obstructive episode. Unfortunately, measurements of leptin and TNF were not made for our patient and, thus, this hypothesis cannot yet be confirmed.

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